Clinical trial results:
Intrathecal morphine administration for minimally invasive pancreatic surgery: A double blind, prospective randomized placebo-controlled trial.

Summary

EudraCT number	2021-002625-20
Trial protocol	BE
Global end of trial date	07 February 2025

Results information

Result version number	v1 (current)
This version publication date	10 April 2025
First version publication date	10 April 2025

Trial information

Trial identification

Sponsor protocol code	SC052021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
Sponsor organisation address	HERESTRAAT 49, Leuven, Belgium, 3000
Public contact	Research Anesthesiology, University Hospitals Leuven, +32 16344270, steve.coppens@uzleuven.be
Scientific contact	Research Anesthesiology, University Hospitals Leuven, +32 16344270, steve.coppens@uzleuven.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 February 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2024
Global end of trial reached?	Yes
Global end of trial date	07 February 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the efficacy of intrathecal morphine after minimally invasive pancreatic surgery

Protection of trial subjects:

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.
The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled "Essential Documents for the Conduct of a Clinical Trial", and as specified by applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 128
Worldwide total number of subjects	128
EEA total number of subjects	128

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	73
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be recruited by the principal investigator or co-investigator. Detailed background information will be given about the study and any question brought forward by the patient will be answered. Each eligible patient willing to participate will sign a written informed consent before any particular study procedure.

Pre-assignment

Screening details:

- 18-80 years of age
- Body Mass Index (BMI) ≤ 40 kg/m2
- Patient is able to give informed consent
- Patient understands the use of morphine PCIA
- Patient is scheduled for elective minimal invasive pancreatic surgery
- ASA I-IV

Period 1

Period 1 title	Surgery (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Patients will be randomized using a computer-generated permuted block randomization sequence (variable block-size, 1:1 allocation). Allocation concealment will be ensured by enclosing assignments in sealed, opaque, sequentially numbered envelopes which will be opened before surgery at the holding area. The study nurse will than prepare the trial medication (see above). If for any reason, either due to perioperative complications or logistic reasons, a patient is withdrawn from the elective pancr

Arms

Are arms mutually exclusive?	Yes
Arm title	ITM (intrathecal morphine)

Arm description:

Before induction of anesthesia, the patient is positioned in the upright position. The skin of the lumbar region will be disinfected with chlorhexidine 0.5%. After careful identification of the lumbar interspace at level L3-L4 or L4-L5 and local anesthesia infiltration with 5 ml lidocaine 1%, an introducer will be inserted via which a 27G Whitacre needle, Pencan© (B.Braun Bethlehem, Pennsylvania, USA) will be advanced until identification of the subarachnoid space. Correct needle placement will be verified by observing spontaneous cerebrospinal fluid (CSF) reflux. After careful aspiration of CSF, the trial medication will be injected. After injection of 1 ml, a second careful aspiration of CSF will confirm further appropriate needle placement. In case of a difficult puncture on 2 levels (L3-L4; L4-L5), a 25G Whitacre needle may be used. ITM dose up 4 µg/kg will be administered + bupivacaine 0.5%

Arm type	Experimental
Investigational medicinal product name	morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

4 µg/kg with a maximum dose of 200 µg if patient > 75 years

Investigational medicinal product name	bupivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

0,125 mg/kg hyperbaric bupivacaine intrathecal morphine

Arm title	Spinal placebo

Arm description:

Before induction of anesthesia, the patient is positioned in the upright position. The skin of the lumbar region will be disinfected with chlorhexidine 0.5%. After careful identification of the lumbar interspace at level L3-L4 or L4-L5 and local anesthesia infiltration with 5 ml lidocaine 1%, an introducer will be inserted via which a 27G Whitacre needle, Pencan© (B.Braun Bethlehem, Pennsylvania, USA) will be advanced until identification of the subarachnoid space. Correct needle placement will be verified by observing spontaneous cerebrospinal fluid (CSF) reflux. After careful aspiration of CSF, the trial medication will be injected. After injection of 1 ml, a second careful aspiration of CSF will confirm further appropriate needle placement. In case of a difficult puncture on 2 levels (L3-L4; L4-L5), a 25G Whitacre needle may be used. Placebo Nacl 0.9% + bupivacaine 0.5% will be injected

Arm type	Placebo
Investigational medicinal product name	bupivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

- The control group will receive placebo (saline 0.9 %) and 0,125 mg /kg hyperbaric bupivacaine 0.5 % (total volume: 4ml).

Number of subjects in period 1	ITM (intrathecal morphine)	Spinal placebo
Started	64	64
Completed	64	64

Baseline characteristics

Reporting groups

Reporting group title	ITM (intrathecal morphine)

Reporting group description:

Before induction of anesthesia, the patient is positioned in the upright position. The skin of the lumbar region will be disinfected with chlorhexidine 0.5%. After careful identification of the lumbar interspace at level L3-L4 or L4-L5 and local anesthesia infiltration with 5 ml lidocaine 1%, an introducer will be inserted via which a 27G Whitacre needle, Pencan© (B.Braun Bethlehem, Pennsylvania, USA) will be advanced until identification of the subarachnoid space. Correct needle placement will be verified by observing spontaneous cerebrospinal fluid (CSF) reflux. After careful aspiration of CSF, the trial medication will be injected. After injection of 1 ml, a second careful aspiration of CSF will confirm further appropriate needle placement. In case of a difficult puncture on 2 levels (L3-L4; L4-L5), a 25G Whitacre needle may be used. ITM dose up 4 µg/kg will be administered + bupivacaine 0.5%

Reporting group title	Spinal placebo

Reporting group description:

Before induction of anesthesia, the patient is positioned in the upright position. The skin of the lumbar region will be disinfected with chlorhexidine 0.5%. After careful identification of the lumbar interspace at level L3-L4 or L4-L5 and local anesthesia infiltration with 5 ml lidocaine 1%, an introducer will be inserted via which a 27G Whitacre needle, Pencan© (B.Braun Bethlehem, Pennsylvania, USA) will be advanced until identification of the subarachnoid space. Correct needle placement will be verified by observing spontaneous cerebrospinal fluid (CSF) reflux. After careful aspiration of CSF, the trial medication will be injected. After injection of 1 ml, a second careful aspiration of CSF will confirm further appropriate needle placement. In case of a difficult puncture on 2 levels (L3-L4; L4-L5), a 25G Whitacre needle may be used. Placebo Nacl 0.9% + bupivacaine 0.5% will be injected

Reporting group values	ITM (intrathecal morphine)	Spinal placebo	Total
Number of subjects	64	64	128
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	28	48
From 65-84 years	44	36	80
85 years and over	0	0	0
Age continuous Units: years			
geometric mean	63.25	66.33	
standard deviation	± 11.4	± 9.64	-
Gender categorical Units: Subjects			
Female	33	34	67
Male	31	30	61

Subject analysis sets	
Subject analysis set title	ITM
Subject analysis set type	Intention-to-treat
Subject analysis set description: Morphine consumption at 24 and 48 hours	
Subject analysis set title	Spinal placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: morphine consumption over 24 and 48 hours	

Reporting group values	ITM	Spinal placebo	
Number of subjects	64	64	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	28	
From 65-84 years	44	36	
85 years and over	0	0	
Age continuous Units: years			
geometric mean	63.25	66.33	
standard deviation	± 11.4	± 9.64	
Gender categorical Units: Subjects			
Female	33	64	
Male	31	30	

End points

End points reporting groups

Reporting group title	ITM (intrathecal morphine)

Reporting group description:

Before induction of anesthesia, the patient is positioned in the upright position. The skin of the lumbar region will be disinfected with chlorhexidine 0.5%. After careful identification of the lumbar interspace at level L3-L4 or L4-L5 and local anesthesia infiltration with 5 ml lidocaine 1%, an introducer will be inserted via which a 27G Whitacre needle, Pencan© (B.Braun Bethlehem, Pennsylvania, USA) will be advanced until identification of the subarachnoid space. Correct needle placement will be verified by observing spontaneous cerebrospinal fluid (CSF) reflux. After careful aspiration of CSF, the trial medication will be injected. After injection of 1 ml, a second careful aspiration of CSF will confirm further appropriate needle placement. In case of a difficult puncture on 2 levels (L3-L4; L4-L5), a 25G Whitacre needle may be used. ITM dose up 4 µg/kg will be administered + bupivacaine 0.5%

Reporting group title	Spinal placebo

Reporting group description:

Before induction of anesthesia, the patient is positioned in the upright position. The skin of the lumbar region will be disinfected with chlorhexidine 0.5%. After careful identification of the lumbar interspace at level L3-L4 or L4-L5 and local anesthesia infiltration with 5 ml lidocaine 1%, an introducer will be inserted via which a 27G Whitacre needle, Pencan© (B.Braun Bethlehem, Pennsylvania, USA) will be advanced until identification of the subarachnoid space. Correct needle placement will be verified by observing spontaneous cerebrospinal fluid (CSF) reflux. After careful aspiration of CSF, the trial medication will be injected. After injection of 1 ml, a second careful aspiration of CSF will confirm further appropriate needle placement. In case of a difficult puncture on 2 levels (L3-L4; L4-L5), a 25G Whitacre needle may be used. Placebo Nacl 0.9% + bupivacaine 0.5% will be injected

Subject analysis set title	ITM
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Morphine consumption at 24 and 48 hours

Subject analysis set title	Spinal placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

morphine consumption over 24 and 48 hours

Primary: Morphine consumption 24 hours

End point title	Morphine consumption 24 hours

End point description:

End point type	Primary

End point timeframe:

Assessed 24 hours post-intubation

End point values	ITM (intrathecal morphine)	Spinal placebo	ITM	Spinal placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	64	64	64	64
Units: milligram(s)/24 hours				
median (inter-quartile range (Q1-Q3))	15 (3.1 to 30.5)	29.75 (13.5 to 45)	15 (3.1 to 30.5)	29.75 (13.5 to 45)

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description: ITM versus Spinal placebo	
Comparison groups	ITM (intrathecal morphine) v Spinal placebo v ITM v Spinal placebo
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Secondary: Next 24 hour morphine consumption

End point title	Next 24 hour morphine consumption
End point description:	
End point type	Secondary
End point timeframe: 48 hour morphine consumption	

End point values	ITM (intrathecal morphine)	Spinal placebo	ITM	Spinal placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	64	64	64	64
Units: milligram(s)/48 hours				
median (inter-quartile range (Q1-Q3))	21.7 (11.1 to 45.14)	36.81 (16.8 to 56.46)	21.7 (11.1 to 45.14)	36.81 (16.8 to 56.46)

Statistical analyses

Statistical analysis title	Key secondary outcome
Comparison groups	ITM (intrathecal morphine) v Spinal placebo v ITM v Spinal placebo

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From enrolment until time of discharge from hospital	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	27
Reporting groups	
Reporting group title	ITM (intrathecal morphine)
Reporting group description: Intrathecal morphine	
Reporting group title	Placebo Spinal
Reporting group description: -	

Serious adverse events	ITM (intrathecal morphine)	Placebo Spinal	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 64 (23.44%)	18 / 64 (28.13%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
surgical leakage			
subjects affected / exposed	15 / 64 (23.44%)	16 / 64 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
respiratory depression			
subjects affected / exposed	11 / 64 (17.19%)	4 / 64 (6.25%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	ITM (intrathecal morphine)	Placebo Spinal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 64 (46.88%)	20 / 64 (31.25%)	

Gastrointestinal disorders PONV subjects affected / exposed occurrences (all)	 21 / 64 (32.81%) 0	 17 / 64 (26.56%) 0	
Skin and subcutaneous tissue disorders pruritus subjects affected / exposed occurrences (all)	 16 / 64 (25.00%) 16	 5 / 64 (7.81%) 5	
Renal and urinary disorders urinary retention subjects affected / exposed occurrences (all)	 1 / 64 (1.56%) 1	 0 / 64 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2022	1) At current our inclusion rate is lagging behind. This is partially due to restrictive exclusion criteria. We envisioned more adverse events in patients with severe liver function disorders, however most adverse events are surgically related, and parameter changes are more related to pancreatic disease. There was also concern that tumor surgery would be more complex (and more conversion to open surgery) in patients with high bilirubin levels, however rigorous pre-operative check-up is more important here. Furthermore, our initial showed us this is not the case. Liver function disease which affects our clotting parameters remains a strict exclusion criterion of course. (Page 13,21) 2) Our renal function exclusion criterion has also been lowered to GFR < 30 to match more closely clinical decision making in hospital when to adjust morphine (Page 13, 21). (Adjusted trial flow chart with specific mention of GFR < 30 mL/min as exclusion criterion) 3) Secondly, recent literature indicates minimal invasive laparoscopic surgery (laparoscopic, robotic or partial) has same postoperative pain issues. (Reference 6 added to protocol, all subsequent references changed number) To increase recruitment and to speed up the evaluation of intrathecal morphine it seemed wise to include other minimal invasive pancreatic surgery procedures. Therefor title and subsequent acronym was changed as reference was added. The title of our RCT will change to "Intrathecal morphine administration for minimally invasive pancreatic surgery: A double blind, prospective randomized placebo-controlled trial", added abbreviation for minimal invasive pancreatic surgery (mips on page 7) (page 1, 2, 11, 14, 27 and all pages containing original title)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported